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Fluorous synthesis of sclerotigenin-type benzodiazepine-quinazolinones

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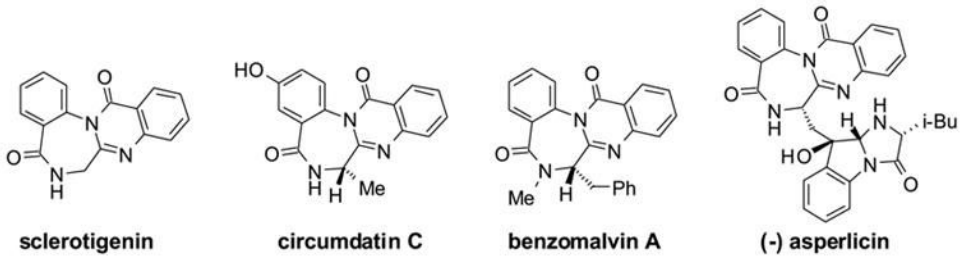
Abstract

A new synthetic protocol for sclerotigenin-type benzodiazepine-quinazolinone library scaffold is introduced. A fluorous benzyl protecting group is used for synthesis of 4-benzodiazepine-2,5-dione intermediate and also as a phase tag for fluorous solid-phase extraction (F-SPE).

Keywords

sclerotigenin; benzodiazepine-quinazolinone; 1,4-benzodiazepine-2,5-dione; fluorous synthesis; solid-phase extraction

Sclerotigenin was isolated from the sclerotia of *Penicillium sclerotigenum* and has shown promising antiinsectan activity.[1] It is the simplest member of the benzodiazepine-quinazolinone natural alkaloid family. Other members in this family such as circumdatins A–G isolated from terrestrial fungus *Aspergillus ochraceus*[2] and benzomalvins A–C isolated from fungus *Penicillium* sp also possess interesting biological activities.[3]



Privileged 1,4-benzodiazepine-2,5-dione ring systems are the key intermediates for synthesis of benzodiazepine-quinazolinone alkaloids.[4] As part of our continuous effort on the development of fluorous synthetic protocols, we have employed a series of fluorous protecting groups for library synthesis.[5,6] Reported here is a new approach to synthesize benzodiazepinedione scaffold using fluorous benzyl as a protecting group and also as a phase tag for fluorous solid-phase extraction (F-SPE).[7] Further derivatization of benzodiazepinediones leads to formation of sclerotigenin ring skeleton.

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Taking the advantage that numbers of conventional solution-phase and solid-phase synthetic methods for benzodiazepine have been reported in literature,[8] we adopted Ellman's solid-phase method for fluorous synthesis (Scheme 1).[9] Fluorous benzaldehyde **1** prepared by reaction of a hydroxybenzaldehyde with a fluorous alcohol was used as the starting material. Compound **2** was produced by reductive amination of **1** with an amino ester. Compound **2** was reacted with an anthranilic acid in the presence of 1-ethyl-3-3-dimethylaminopropyl)carbodiimide (EDCI) and *N*-methylpyrrolidine (NMP). The 1,4-benzodiazepine-2,5-dione ring formation was accomplished by base-promoted cyclization of **3**. Compounds **2**, **3,** and **4** generated in this reaction sequence were purified by simple workup or F-SPE with Fluoro*Flash*® cartridges.[10] In F-SPE, the first wash with 80:20 MeOH–H_2O eluted the non-fluorous components. The desired fluorous compound was eluted with 100% MeOH. A total of nine analogs of compound **4** with substitution variations (R1 and R^2) were prepared.[11]

With nine different benzodiazepinediones **4** in hand, we then conducted parallel synthesis to construct the quinazolinone ring skeleton (Scheme 2).[1c] Compound **4** was acylated with 2-nitrobenzoyl chloride in the presence of *t*-BuN=P(NMe_2)$_3$ as a base to give compound **5** (Table 1). If substituted 2-nitrobenzoyl chloride was employed for acylation, the third diversity point (R3) could be introduced. Compounds **5** were purified by automated RapidTrace F-SPE.[12] The nitro group of **5** was reduced with zinc dust in acetic acid under sonication conditions. Resulted amino group simultaneously underwent cyclization to form quinazolinone ring of **6**. The parallel sonication reactions of **5** gave the reduction/cyclization products **6** in a broad range of yield (21–73%). Since some reactions had low yields, F-SPE was not sufficient for purification. Reverse-phase chromatography was applied to purify compounds **6**. The capability to purify fluorous compounds by non-fluorous technique is a useful option. It could be a difficult task in solid-phase synthesis to separate resin-bound impurities. At the last step, F-benzyl tag of compounds **6** was removed by treated with 90:5:5 TFA-H_2O-dimethylsulfide (DMS) under microwave radiation, followed by F-SPE on RapidTrace® workstation to give the final product **7** with the sclerotigenin ring skeleton.[13]

In summary, we have developed a new approach for the synthesis of fluorous 1,4-benzodiazepine-2,5-diones. The key intermediates can be readily converted to sclerotigenin ring skeleton. The new method which produces the library scaffold with substitution variation coupled with the simple F-SPE separation is an alternative way for solution-phase parallel synthesis of benzodiazepine-quinazolinone analogs.

Acknowledgements

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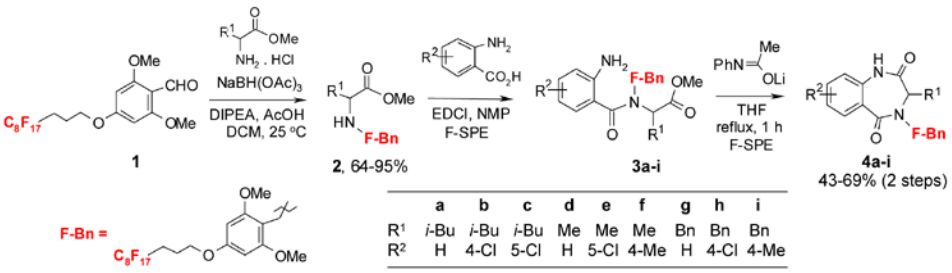
References

1. a) Penhoat M, Bohn P, Dupas G, Papamicael C, Marsais F, Levacher V. Tetrahedron Asymm 2006;17:281–286. b) Liu JF, Kaselj M, Isome Y, Chapnick J, Zhang B, Bi G, Yohannes D, Yu L, Baldino CM. J Org Chem 2005;70:10488–10493. [PubMed: 16323862] c) Grieder A, Thomas AW. Synthesis 2003:1707–1711. d) Snider BB, Busuyek MV. Tetrahedron 2001;57:3301–3307. e) He F, Foxman BM, Snider BB. J Am Chem Soc 1998;120:6417–6418.
2. Rahbaek L, Breinholt J. J Nat Prod 1999;62:904–905. [PubMed: 10395516]
3. a) Sun HH, Barrow CJ, Sedlock DM, Gillum AM, Cooper R. J Antibiotics 1994;47:515–522. [PubMed: 7518818] b) Sugimori T, Okawa T, Eguchi S, Kakehi A, Yashima E, Okamoto Y. Tetrahedron 1998;54:7997–8008.
4. Horton DA, Bourne GT, Smythe ML. Chem Rev 2003;103:893–930. [PubMed: 12630855]
5. a) Zhang W, Lu Y, Chen CH-T, Zeng L, Kassel DB. J Comb Chem 2006 8:687–695. b) Zhang W, Lu Y, Chen CH-T, Curran DP, Geib S. Eur J Org Chem 2006:2055–2059. c) Zhang W, Lu Y, Geib S. Org Lett 2005;7:2269–2272. [PubMed: 15901186] d) Zhang W, Chen CHT. Tetrahedron Lett

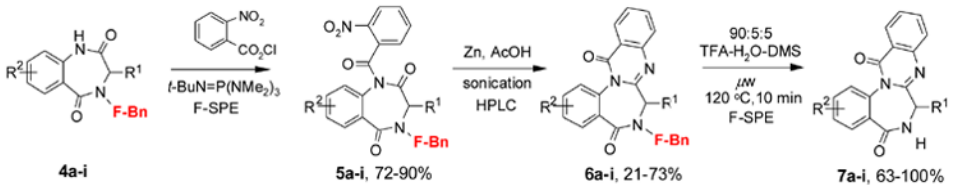
2005;46:1807–1810. [PubMed: 18079977] e) Lu Y, Zhang W. Mol Diversity 2005;9:91–98. f) Nagashima T, Zhang W. J Comb Chem 2004;6:942–949. [PubMed: 15530122] g) Lu Y, Zhang W. QSAR Comb Sci 2004;23:827–835. h) Zhang W, Tempest P. Tetrahedron Lett 2004;45:6757–6760. i) Zhang W, Lu Y. Org Lett 2003;5:2555–2558. [PubMed: 12841779] j) Chen CHT, Zhang W. Org Lett 2003;5:1015–1017. [PubMed: 12659562] k) Zhang W. Org Lett 2003;5:1011–1014. [PubMed: 12659561] l) Zhang W, Luo Z, Chen CH-T, Curran DP. J Am Chem Soc 2002;124:10443–10450. [PubMed: 12197746]

6. Selected reviews on fluorous synthesis. a) Curran DP. Aldrichemica Acta 2006;39:3–9.b) CurranDPGladyszJACurranDPHorvathITHandbook of Fluorous ChemistryWiley-VCHWeinheim2004101127 c) Zhang W. Chem Rev 2004;104:2531–2556. [PubMed: 15137799] d) Zhang W. Curr Opin Drug Discov Develop 2004;7:784–797. e) Zhang W. Tetrahedron 2003;59:4475–4489. f) Curran DP. Angew Chem Int Ed Eng 1998;37:1174–1196.
7. For reviews on F-SPE, see a) Zhang W, Curran DP. Tetrahedron 2006;62:11837–11865.b) CurranDPGladyszJACurranDPHorvathITHandbook of Fluorous ChemistryWiley-VCHWeinheim2004101127 c) Curran DP. Synlett 2001:1488–496.. See also d) Zhang W, Lu Y, Nagashima T. J Comb Chem 2005;7:893–897. [PubMed: 16283798]
8. For a recent review on solid-phase synthesis of benzodiazepines, see Kamal A, Reddy KL, Devaiah V, Shankaraiah N, Reddy DR. Mini-Rev Med Chem 2006;6:53–68. [PubMed: 16457632]
9. Boojamra CG, Burow KM, Thompson LA, Ellman JA. J Org Chem 1997;62:1240–1256.
10. Fluoro*Flash*® SPE cartridges are available from Fluorous Technologies, Inc. (www.fluorous.com)
11. A general procedure for the synthesis of compounds **2** and **4**. To a solution of leucine methyl ester hydrochloride (7.6 g, 42 mmol), 2,6-dimethoxy-4-[3-(perfluorooctyl)propyloxy]benzaldehyde **1** (26 g, 40 mmol), and *N*,*N*-diisopropylethylamine (7 mL, 0.04 mol) in CH_2Cl_2 (0.3 L) was added 4 Å molecular sieves (3 g) at 23 °C. $NaBH(OAc)_3$ (13 g, 60 mmol) was added after 4 h, then water was added after additional 3 h. The CH_2Cl_2 layer was washed with aq. NH_4Cl and brine. After most of the solvent was removed using a rotary evaporator, the residue was passed through a pad of silica gel (50 mL). The product was eluted with hexanes–EtOAc (1:1, 300 mL). The concentrated product was further triturated with hexanes–Et_2O to give the desired compound **2** (R^1 = *i*-Bu, 3.9 g, 95% yield). ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.08 (s, 2H), 4.02 (t, 2H, J = 5.8 Hz), 3.78 (s, 6H), 3.59 (s, 3H), 3.26 (t, 1H, J = 7.1 Hz), 2.45–2.00 (m, 5H), 1.82–1.35 (m, 3 H), 0.88 (d, 3H, J = 6.5 Hz), 0.81 (d, 3H, J = 6.4 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.4, 159.3, 108.9, 90.7, 66.3, 59.0, 55.5, 51.3, 42.8, 39.9, 28.2, 27.9, 27.5, 24.8, 22.6, 22.0, 20.5. LC-MS (APCI+) *m/z* 772 $[M+1]^+$. To a solution of **2** (R^1 = *i*-Bu, 4.3 g, 5.6 mmol) in *N*-methylpyrrolidine (30 mL), 4-chloroanthranilic acid (1.9 g, 11 mmol) and EDCI-HCl (2.1 g, 11 mmol) were added as solid at 23 °C. The same amounts of the acid and EDCI-HCl were added after 2 h and 4 h. One day after the final addition, the reaction mixture was diluted with DMSO (300 mL), and was loaded onto an F-SPE cartridge (50 g), and the flask was rinsed with DMSO (100 mL), and was loaded to the silica gel. The nonfluorous components were eluted with MeCN–H_2O (1:1, 300 mL, and 4:1, 200 mL), and then most of the solvent was drained from the cartridge. The amide coupling product was eluted with MeCN (0.4 L). The MeCN solution was concentrated in a rotary evaporator, and the residue was treated with a solution of lithium acetanilide (0.33 M in THF, 30 mL). The mixture was refluxed for 1 h. After cooling, AcOH (0.6 mL) was added, and the solvent was removed in a rotary evaporator. MeOH (30 mL) was added to the residue, and it was heated until the solvent started to boil. The mixture was left at 23 °C for 1 d, and product **4b** (R^1 = *i*-Bu, R^2 = 4-Cl) was collected as a solid by filtration (3.5 g, 69% yield based on the amount of **2**). ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.16 (dd, J = 7.1, 1.9 Hz 1,), 6.90 (d, J = 1.8 Hz, 1H), 6.09 (s, 2H), 5.23 (d, J = 13.8 Hz, 1H), 4.56 (d, J = 13.8 Hz, 1H), 4.15–3.85 (m, 3H), 3.75 (s, 6H), 2.45–2.00 (m, 4H), 1.60–1.45 (m, 1H), 1.35–1.15 (m, 2H), 0.80 (d, J = 6.4 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H). ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 173.5, 165.1, 160.6, 160.1, 137.7, 136.2, 133.3, 125.5, 124.6, 119.4, 104.1, 90.6, 66.3, 59.5, 55.5, 42.0, 38.3, 27.9 (t, J = 22 Hz), 25.2, 22.3, 22.1, 20.5. LC-MS (APCI +) *m/z* 893 $[M+1]^+$.
12. Zhang W, Lu Y. J Comb Chem 2006;8:890–896. [PubMed: 17096578]
13. A general procedure for the synthesis of compounds **5, 6**, and **7**. To a solution of **4** in CH_2Cl_2 was added *t*-butylimino-tris(dimethylamino)phosphorane (10 equiv) and 2-nitrobenzoic acid (2 equiv). The reaction mixture was stirred for 10 min and then concentrated in a rotary evaporator. The residue was dissolved in DMF (1 mL) and purified on RapidTrace® SPE workstation with 2 g cartridges to afford **5** in 72–90% yield. A solution of **5** in acetic acid (1 mL) was added Zn dust (20 equiv) and

sonicated at room temperature for 2 h. The Zn was filtered and the filtrate was diluted with EtOAc and washed with $NaHCO_3$ and brine. The EtOAc solution was dried and concentrated in a rotary evaporator. The residue was dissolved in MeCN and purified by C18 HPLC to afford **6** in 21–73% yields. A solution of **6** in TFA-H_2O-DMS (90:5:5) was stirred for 3 days before being concentrated in a rotary evaporator. The residue was dissolved in DMF (1 mL) and purified by RapidTrace® SPE workstation to afford **7** in 63–100% yields. Analytical date for compound **7b** (R^1 = *i*-Bu, R^2 = 4-Cl): ^{1}H NMR (275 Hz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 1.80–2.05 (m, 2H), 2.05–2.25 (m, 1H), 4.10–4.35 (m, 1H), 6.66 (d, J = 6.2 Hz, 1H), 7.45–7.59 (m, 2H), 7.67 (d, J = 1.9 Hz, 1H), 7.70–7.85 (m, 2H), 7.91 (d, J = 8.4 Hz, 1H), 8.31 (dd, J = 1.4, 8.0 Hz, 1H); ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 22.0, 23.1, 24.3, 38.0, 52.4, 121.3, 127.5, 127.8, 127.9, 128.7, 128.9, 129.5, 131.0, 134.3, 135.2, 137.4, 146.0, 154.1, 161.5, 167.1; LCMS (APCI+) 368 $[M+1]^+$.



Scheme 1.
Fluorous synthesis of benzodiazepinedione **4**



Scheme 2.
Parallel synthesis of nine benzodiazepine-quinazolinones **7**

Table 1

Yields for analogs of compounds **5**, **6**, and **7**

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
R^1	*i*-Bu	*i*-Bu	*i*-Bu	Me	Me	Me	Bn	Bn	Bn
R^2	H	4-Cl	5-Cl	H	5-Cl	4-Me	H	4-Cl	4-Me
5a–i	82%	80%	90%	75%	94%	90%	75%	72%	81%
6a–i	44%	50%	67%	21%	51%	62%	70%	65%	73%
7a–i	83%	86%	91%	91%	63%	71%	100%	89%	97%